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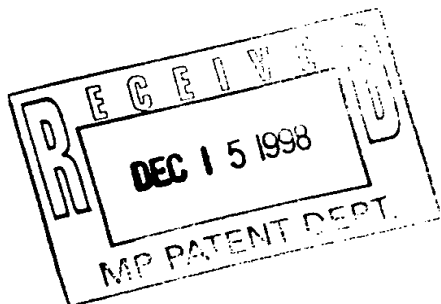
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54 Fast release solid preparation of dihydropyridine A compound and process for preparing it.

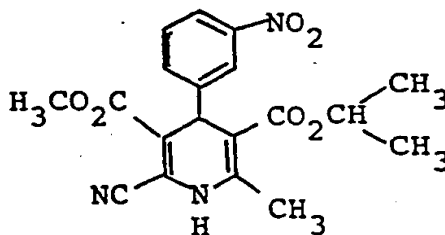
57 A fast release solid preparation, which comprises solid dispersion composition containing dihydropyridine A compound and hydroxypropylmethyl cellulose and process for preparing it.



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FAST RELEASE SOLID PREPARATION
OF DIHYDROPYRIDINE A COMPOUND AND PROCESS FOR
PREPARING IT

The present invention relates to the fast release solid preparation comprising dihydropyridine A compound [isopropyl 6-cyano-5-methoxycarbonyl-2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate], which is represented by the following chemical formula:



Dihydropyridine A compound shows vasodilating activities such as coronary vasodilating activity, hypotensive activity or the like, and hence is useful for the treatment of coronary vascular diseases such as

cardiac incompetence, angina pectoris, myocardial infarction or the like, or hypertension.

However, when orally administered, the ratio of the absorption of dihydropyridine A compound into blood to its dose is insufficient owing to its sparing solubility into water (practically insoluble) and so dihydropyridine A compound has the disadvantage of its poor bioavailability.

The inventors of the present invention have discovered that said disadvantage could be overcome by dispensing dihydropyridine A compound with hydroxypropylmethyl cellulose, a water-soluble polymer, to prepare solid dispersion composition and completed the present invention.

The present invention is explained in more detail in the following.

The solid dispersion composition of the present invention can be prepared⁺, for example, by dissolving dihydropyridine A compound in suitable organic solvent, adding a water-soluble polymer, hydroxypropylmethyl cellulose, to the resultant solution to prepare homogeneous suspension, and then evaporating the organic solvent according to the conventional manner.

The organic solvents to be used in this procedure are not restrictive and any solvent, wherein dihydropyridine A compound can be dissolved, can be used. Suitable examples of said solvent may include chloroform, methylene chloride, acetone, ethyl acetate, alcohol (e.g. methanol, ethanol, etc.) and the like.

Hydroxypropylmethyl cellulose is one of the water-soluble polymers and it is used to disperse dihydropyridine A compound to form solid dispersion composition.

⁺ by reacting dihydropyridine A compound with hydroxypropylmethyl cellulose,

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5 The quantity of hydroxypropylmethyl cellulose to be used is not restrictive and any quantity, by which dihydropyridine A compound can be dispersed, can be used and preferably three to seven times as much as dihydropyridine A compound by weight are used.

10 The solid dispersion composition of the present invention prepared by aforesaid procedure can be used by itself as fast release solid preparation and may be converted into various dosage forms such as powders, fine granules, granules, tablets or the like, according to the conventional manner. If desired, coloring agents, sweetening agents, flavouring agents, diluents (e.g. sucrose, lactose, starch, crystalline cellulose, 15 low-substituted hydroxypropyl cellulose, synthetic aluminium silicate, etc.), lubricant (e.g. magnesium stearate, etc.) or the like, may be dispensed with said solid dispersion composition.

20 The solid dispersion composition and the various preparations of the present invention, which are prepared by optionally converting said solid dispersion composition into various dosage forms as mentioned above, have remarkably improved solubility and absorptivity into blood in comparison with dihydropyridine 25 A compound bulk.

30 If desired, in order to enhance the stability, add a beauty, smooth the surface, improve the ease of the administration and the like, the solid dispersion composition as prepared above can be used, for example, as a film-coated tablet.

35 Said film-coated tablet can be prepared by coating the aforementioned tablet according to the conventional method, wherein the coating layer may include hydroxypropylmethyl cellulose.

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To show the usefulness of the fast release solid preparation of the present invention, the test results are explained as follows.

5 Dissolution Test

[Test Sample]

- (1) The fine granules disclosed in the following
Example 2
- (2) The tablet disclosed in the following Example 3
- 10 (3) The film-coated tablet disclosed in the following
Example 4.

[Test Method]

15 The tests were carried out according to the
method 2 (paddle method) of the dissolution test in
The Pharmacopoeia of Japan (tenth edition) using water
as test solution and the dissolution rate after 15
minutes from the beginning of each dissolution test
was measured.

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[Test Results]

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Test Sample	Dissolution rate (%)
(1)	100
(2)	100
(3)	100

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From the results of the dissolution test, it turned out that any solid preparation comprising the solid dispersion composition of dihydropyridine A compound exhibited extremely good dissolution velocity.

Plasma Concentration Test

[Test Sample]

- 5 (1) The tablet disclosed in the following Example 3
(This tablet contains 2 mg of dihydropyridine A
compound in one tablet.)
- 10 (2) The reference tablet :
Tablets, each of which had the composition as
explained below, were prepared by the conventional
method (wet granulating method) and they were
used as the reference tablets in this test.

Composition

	Dihydropyridine A compound (micro powder)	10 mg.
	Lactose	88.5 mg
15	Low-substituted hydroxypropyl cellulose	30 mg
	Sodium lauryl sulfate	3 mg
	Hydroxypropylmethyl cellulose	3 mg
	Magnesium stearate	0.5 mg

20 [Test Method]

The amount of tablets equivalent to 10 mg of
dihydropyridine A compound [i.e. 5 tablets of Test
Sample (1) and 1 tablet of Test Sample (2)] was orally
administered to six beagle dogs (8-12 kg), which had
25 been withheld from any food overnight in a crossover
design. The plasma concentration of dihydropyridine
A compound was determined by gas chromatography with
ECD at 0.5, 1, 2, 4, 6, 8, 10, 12 and 24 hours after
administration.

30

[Test Results]

The plasma concentration at each time, the
maximum plasma concentration (C max) and the area
under the plasma concentration time curve (AUC) in
35 each case of Test Sample (1) and Test Sample (2) are

shown in the following table.

Each value is represented by [the mean value
± standard error] for six beagle dogs.

Test Sample	Plasma concentration (ng/ml)					
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr
(1)	133.6 ±20.4	95.1 ±10.4	45.8 ±5.0	19.6 ±2.7	12.7 ±1.8	9.6 ±1.5
(2)	34.1 ±6.4	59.8 ±7.2	41.0 ±6.5	17.6 ±2.1	10.8 ±1.3	7.3 ±0.9

Test Sample	Plasma concentration (ng/ml)			C max (ng/ml)	A U C (ng·hr/ml)
	10 hr	12 hr	24 hr		
(1)	7.7 ±1.1	6.9 ±1.1	1.2 ±0.6	133.6 ±20.4	361.1 ±47.4
(2)	5.9 ±0.8	4.3 ±0.6	0.3 ±0.3	59.8 ±7.2	238.9 ±27.2

As clear from the table, with respect to both
the maximum plasma concentration and the area under
the plasma concentration time curve, Test Sample (1)
was proved to be significantly superior to Test Sample
(2).

Namely, it turned out that by dispensing
dihydropyridine A compound with hydroxypropylmethyl
cellulose to form solid dispersion composition, the
absorptivity of dihydropyridine A compound into blood
was remarkably improved and that its bioavailability
was extremely enhanced.

The present invention is explained according to the following Examples.

Example 1

5 Dihydropyridine A compound (100 g) was dissolved in anhydrous ethanol (5 l) and then hydroxypropylmethyl cellulose (500 g) was added thereto to prepare a suspension. Then the organic solvent was evaporated under reduced pressure to give solid dispersion
10 composition.

Example 2

15 To a suspension of dihydropyridine A compound (100 g) and hydroxypropylmethyl cellulose (500 g) in anhydrous ethanol (5 l) was added sucrose (9.4 kg) and the resultant mixture was stirred. Then the organic solvent was evaporated under reduced pressure to give solid dispersion composition.

20 This solid dispersion composition was converted into fine granules by the conventional method.

Example 3

25 To a suspension of dihydropyridine A compound (100 g), and hydroxypropylmethyl cellulose (500 g) in anhydrous ethanol (5 l) were added lactose (6.87 kg) and low-substituted hydroxypropyl cellulose (1.5 kg) and the resultant mixture was stirred and then the organic solvent was evaporated under reduced pressure to give solid dispersion composition.

30 After the resultant solid dispersion composition was converted into granules by the conventional method, the granules were converted with magnesium stearate (30 g) into tablets by the conventional method, each weight of which was 180 mg.
35

Example 4

For each tablet given in the Example 3, the coating layer consisting of hydroxypropylmethyl cellulose (5.1 mg), titanium dioxide (1.6 mg),
5 polyethylene glycol-6000 (0.8 mg), talc (0.4 mg) and iron oxide yellow (0.1 mg) was film-coated by the conventional method, to give a film-coated tablet containing dihydropyridine A compound.

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What we claim is :

1. A fast release solid preparation, which comprises
solid dispersion composition containing dihydropyridine
A compound and hydroxypropylmethyl cellulose.
2. A fast release solid preparation of claim 1,
wherein the dosage form is a tablet.
3. A tablet of claim 2,
wherein its surface is film-coated.
4. A fast release solid preparation of claim 1,
wherein dihydropyridine A compound and
hydroxypropylmethyl cellulose are in the ratio of
1:3 to 1:7 by weight.
5. A process for preparing a solid dispersion
composition which comprises reacting dihydropyridine
A compound with hydroxypropylmethyl cellulose.